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A Review on Huntington's Disease

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Huntington's disease (HD) is a devastating neurodegenerative disorder that occurs in patients with a mutation in the huntingtin or IT15 gene. Patients are plagued by early cognitive signs, motor deficits, and psychiatric disturbances. Symptoms are attributed to cell death in the striatum and disruption of cortical–striatal. Mechanisms of cell death are unclear, but processes involving mitochondrial abnormalities, excitotoxicity, and abnormal protein degradation have been implicated. Many factors likely contribute to neuron death and dysfunction and this has made it difficult to systematically address the pathology in HD. Pharmaceutical therapies are commonly used in patients to treat disease symptoms. These have limited benefit and do not address the inexorable disease progression. Several neuroprotective therapies are being evaluated in animal models of HD as well as in clinical trials. Similarly, cell replacement strategies such as fetal transplantation have been used in the clinic with minimal success, making future cell replacement strategies such as stem cell therapy uncertain. This review describes the disease pathology and neurochemistry of HD and addresses many of the past and emerging therapeutic strategies.

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I. Introduction

Huntington's disease is a genetic, progressive, neurodegenerative disorder characterized by the gradual development of involuntary muscle movements affecting the hands, feet, face, and trunk and progressive deterioration of cognitive processes and memory (dementia). Neurologic movement abnormalities may include uncontrolled, irregular, rapid, jerky movements (chorea) and athetosis, a condition characterized by relatively slow, writhing involuntary movements (Novak MJ, *et al.,* Huntington's disease. BMJ.2010). Dementia is typically associated with progressive disorientation and confusion, personality disintegration, impairment of memory control, restlessness and

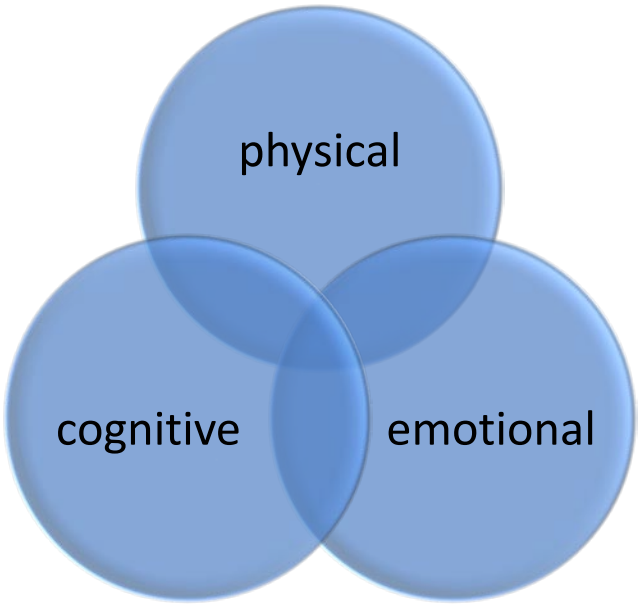

Fig. 1: Difficult Behaviors In Huntington's Disease

II. Epidemiology

Huntington's disease is currently found in many different countries and ethnic groups around the world. There are varying rates of prevalence in different racial groups 2. HD has a worldwide prevalence of five to 288 eight per 100,000 people with no gender preponderance. The highest frequencies of HD are found in Europe and countries of European origin. The lowest frequencies are documented in Africa, China, Japan, and Finland.

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a) Symptoms

The symptoms of HD vary widely from person to person, even within the same family. For some, involuntary movements may be prominent even in the early stages. For others, these may be less evident and emotional and behavioral symptoms may be more obvious. The following are common features of HD:

b) Motor Symptoms

Motor Symptoms Physical symptoms may initially consist of "nervous" activity, fidgeting, twitching, or excessive restlessness. Handwriting may change and facial grimaces may appear. Day-to-day skills involving coordination and concentration, such as driving, become more difficult. These initial symptoms will gradually develop into more marked involuntary movements of the head, trunk and limbs – which often lead to problems in walking and balance. Speech and swallowing can become impaired. Movements generally tend to increase during voluntary effort, stress or excitement, and decrease during rest and sleep.

c) Cognitive Symptoms/ Intellectual Symptoms

Slight intellectual changes are often the first signs of cognitive disturbance. Short-term memory loss may occur while long-term memory generally stays intact. Disorganisation as a result of difficulties with planning, initiating, and organising thoughts, activities, and communication; perseveration; impulsivity; perceptual distortions; lack of insight; distractibility; difficulty in learning new information (Rothlind J *et al.;* 1993).

d) Psychiatric//Behavioral Symptoms

Depression, obsessive-compulsive disorders, anxiety, irritability, apathy, hyper sexuality (uncommon), psychosis (uncommon), Some people can experience depression for a period of months or even years before it is recognized to be an early symptom of Huntington's. Behavioral changes may include aggressive outbursts, impulsiveness, mood swings, and social withdrawal. Often, existing personality traits will be exacerbated by HD, e.g., a person who had a tendency to be irritable. Schizophrenia and other serious psychiatric problems are uncommon in HD but do occur.

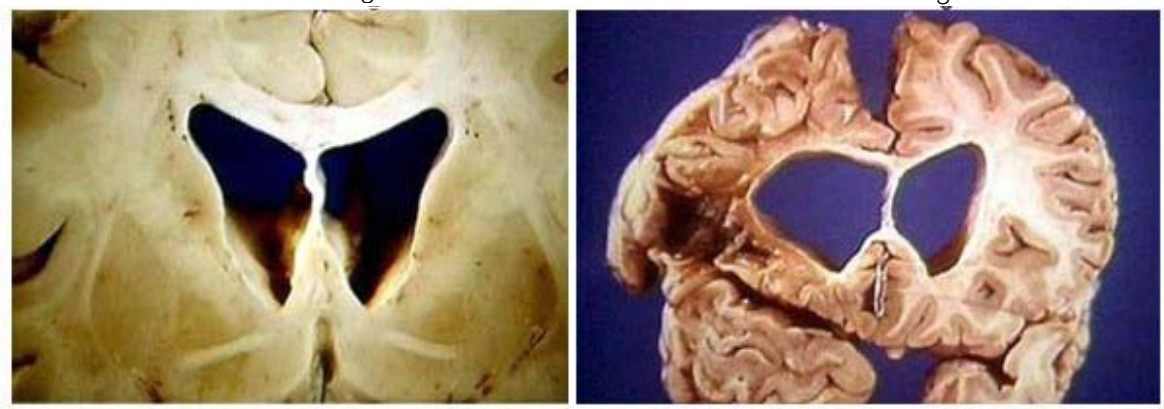
e) Metabolic

Weight loss, sleep disturbance

III. Neuropathology of Huntington's Disease

The specific symptoms and progression of HD can be related to its pathology, which is characterized by the loss of specific neuronal populations in many brain regions. Motor dysfunction in HD results from the disruption of basal ganglia-thalamocortical pathways regulating movement control (Garrett EA, *et al*., 1990 and Graybiel AM. 1990). The primary site of neuronal loss and atrophy in HD brain is in the caudate- putamen (Browne SE, 1999) Vulnerability in HD. The striatum is composed of a variety of medium to large neurons that differ in their size and dendritic profile as well as neurochemical content and output. Severe loss of medium sized striatal neurons was seen in the HD brain. They have large dendritic tree and use GABA as their neurotransmitter (Hassel B, *et al*., 1995).

Normal Basal Ganglia VS. HD Basal Ganglia



The basal ganglia of the human brain, showing the impact of HD on brain structure in this region. Note especially that the brain of a person with HD has bigger openings due to the death of nerve cells in that region

a) Effect of HD on Basal Ganglia

As these neurons degenerate in HD, the neurochemical they contain, including glutamic acid decarboxylase (GAD), substance-P, enkephalin, calcineurin, calbindin, adenosine receptors and dopamine receptors, also decrease. Number of theories has been presented, to determine the exact events involved in the progression of cell deaths caused by HD. One theory proposes that neurons die in HD because of an over-accumulation of normal excitatory chemicals

involved in nerve impulses. Excitatory neurotransmitters (mainly glutamate) are normally present in the brain, but, if they are released in excessive amounts or if brain cells are weak, these excitatory chemicals can cause cell damage and become chemicals known as "excitotoxins." Studies show that when glutamate is injected into the basal ganglion region of brains of living rats, the rats exhibit symptoms of HD (Reddy HP, *et al*., 1999). This first theory had to be modified when high levels of glutamate were not found in the brains of all HD patients. The mitochondrial dysfunction plays a role in pathogenesis of HD. The mitochondria of striatal cells may be damaged with the onset of HD. Scientists today believe that the damaged mitochondria of people with HD make striatal cells unable to produce as much energy as they need, which then makes the cells more susceptible to normal levels of glutamate (Beal MF. 2000). Another theory to explain the death of nerve cells postulates that the cells actually kill themselves in response to chemical changes caused by HD. HD triggers the early death of neurons by accelerating a normal process called apoptosis (Gutekunst AC, *et al*., 2000). 3-Nitropropionic acid and malonate also induce apoptotic profiles and induce pro-apoptotic proteins (Hickey MA, *et al*., 2003). To sum up, the neurobiological effects of HD appear to be the result of a number of different changes that ultimately go out of control. Many studies have shown that neurodegeneration is not confined to the basal ganglia but also occurs widely in cortical and other sub cortical regions.

b) Pathogenesis of Huntington's Disease and Huntingtin Protein

Huntington's disease is caused by the abnormal expansion of a CAG-trinucleotide repeat in the N-terminal exon 1 of the huntingtin gene, which is located on the short arm of chromosome 4 (4p16.3) (The Huntington's Disease Collaborative Research Group. 1993; Brouillet, E. *et al.,* 1999; Brennan, W.A. *et al.,* 1985). In the translated protein, huntingtin, this repeat encodes an expanded polyglutamine repeat sequence. Asymptomatic individuals have the wild type huntingtin gene with 29 or fewer CAG repeats, while HD is caused by expansions of 36 or more repeats (Rubinsztein, D C, *et al.,* 2002; Rubinsztein, D.C. *et al.,* 1996). There is an inverse relationship between the genomic CAG repeat size of the mutant huntingtin gene and the age of onset of signs. The larger the number of CAG repeats, the earlier the age of disease onset. Most adult-onset cases have CAG repeat sizes ranging from 40-50, whereas expansions of more than 55 repeats frequently cause the juvenile form of the disease (Vonsattel, J.P. *et al.,* 1998). Since the discovery of the huntingtin gene, an explosion of research has led to many insights into the normal function of huntingtin and the molecular basis of the disease. The normal or wild type huntingtin protein is found mainly in the cellular cytoplasm. This cytoplasmic protein is ubiquitously and widely expressed in many different tissues but its expression is highest in neurons. Huntingtin protein has been found in vesicle membranes, the cytosol, the nucleus, mitochondria, and microtubules. It appears to be associated with clathrin through huntingtin-interacting protein (HIP-1) (DiFiglia, M. *et al.,* 1995; Panov, A.V. *et al.,* 2002; Trottier, Y. *et al.,* 1995). These intracellular locations suggest that huntingtin may act as a molecular scaffold regulating several cellular processes including clathrin-mediated endocytosis, vesicle transport, synaptic transmission, transcriptional events and mitochondrial function (Rubinsztein, D.C. 2002; Young, A.B. 2003; Harjes, P. et al., 2003; Metzler, M. et al., 2001; Waelter, S. et al., 2001; Sugars, K.L. 2003. Furthermore, huntingtin can protect neuronal cells from apoptotic stress and therefore may have a pro-survival role as well (Rigamonti, D. et al., 2000; Leavitt, B.R. *et al.,* 2001). The number of huntingtin interacting proteins identified up to now exceeds 25 (Li, S.H. *et al.,* 2004. Collectively, the role of huntingtin is complex and it appears to be involved in various cellular functions both in the cytoplasm and nucleus (reviewed in (Li, S.H. *et al.,* 2004). The precise function of normal huntingtin is not yet fully understood and how mutant huntingtin exerts harmful effects remains unclear (Young, A.B. 2003). Various hypotheses have been proposed. For example, the mutant huntingtin protein may be neurotoxic through transcriptional dysregulation or it may make neurons susceptible to excitotoxicity, associated with an increase in cytosolic calcium (Harjes, P. et al., 2003; Bossy-Wetzel, E. et al., 2004). Moreover, mutant huntingtin also dysregulates mitochondrial homeostasis early in the disease (Panov, A.V. *et al.,* (2002) that may cause the release of cytochrome c and the activation of caspases. These proteins are involved in apoptosis (Rangone, H. *et al.,* (2004). Evidence is accumulating of both a toxic effect of mutant huntingtin fragments and a depletion of wild type huntingtin as part of the pathogenesis in HD (Friedlander, R. 2003; Rigamonti, D. *et al.,* 2000; Chen, M. *et al*., 2000; Ona, V. *et al.,* 1999; Sanchez, I. *et al.,* 1999; Zuccato, C. *et al.,* 2001; Landles, C. *et al.,* 2004). Neurons of HD patients contain one copy of the wild type huntingtin allele and one copy of the mutant huntingtin allele. Possibly as part of normal proteolysis of huntingtin, a N-terminal fragment containing the expanded polyglutamine repeat is released. This expanded polyglutamine-containing fragment then undergoes a conformational change and this ultimately, through as yet unknown steps and structures, results in toxic protein aggregates *that* also recruit other proteins (Gutekunst, C.A. *et al.,* 2002; Ona, V. *et al.,* 1999; Wellington, C.L. *et al.,* 2000; Hackam, A.S. *et al.,* 1998; Li, S.H. *et al.,* 2000; Mende-Mueller, *et al.,* 2001). These huntingtin aggregates can be found in any part of a neuron, but primarily in the nucleus

(Harjes, P. *et al.,* 2003; Li, S.H. *et al.,* 2004). Huntingtin protein aggregates become ubiquinated, presumably because they are recognized as misfolded proteins that become targeted for proteasomal degradation. The process of toxic aggregate formation may thus be critical for the development of neuronal dysfunction and degeneration in HD (Gutekunst, C.A. *et al.,* 2002). However, a direct causative pathway from the huntingtin gene mutation to the neostriatal degeneration has not yet been established. For example, it is not clear whether the formation of cytoplasmic aggregates and nuclear inclusions, the presence of soluble aberrant mutant huntingtin fragments, or an intermediary structure is the crucial determinant of neuronal cell death and disease initiation and progression. Several other mechanisms that may contribute to neuronal dysfunction and cell death in HD, which are not directly related to mutant huntingtin, have been proposed to play a role in the disease process. These include impaired energy metabolism by mitochondrial dysfunction, glutamate-mediated excitotoxicity, oxidative stress, altered gene transcription abnormal protein interactions and inappropriate apoptosis (Landles, C. *et al.,* 2004; Ho, L.W. *et al.,* 2001). In neurons with compromised energy metabolism, the threshold for glutamate toxicity is reduced. This leads to activation of glutamate-mediated excitotoxicity, whereas induced oxidative stress increases the production of damaging and free oxygen and nitrogen radicals. Mitochondrial dysfunction also causes the release of cytochrome c and activates caspases, and thus, could be a central phenomenon in HD pathogenesis as it would explain the oxidative stress, excitotoxic processes and energy metabolism dysfunction observed in HD patients (Rangone, H. *et al.,* 2004). How cells die in HD is not clear and whether the dying cells have been dysfunctional for a considerable time before cell death is also unknown. The problem that investigators face is to distinguish primary from secondary events in elucidating the pathogenesis of HD. For now it is not clear whether mitochondrial dysfunction is a primary change or a consequence of the early neuropathological changes in HD (Rubinsztein, D.C. 2002; Landles, C. *et al.,* 2004; Bates, G.P. *et al.,* 2002; Bates, G.2003; Jones, L., 2002). The pathogenesis of HD could well be multifactorial as is the huntingtin protein, which may have many functions.

c) Apoptosis and Huntington's Disease

HD is caused by an abnormal expansion of a CAG-trinucleotide repeat in the huntingtin gene but the precise mechanism of the selective neurodegeneration in HD neostriatum remains unclear. It has been suggested that aberrant apoptosis is involved in the pathogenesis of Huntington's disease (HD) (Wellington, C.L. *et al.,* 1997; Petersén, Å. *et al.,* 1999). Initial studies demonstrated an increase in DNA degradation and (Thomas, L.B. *et al.,* 1995; Dragunow, M. *et al.,* 1995; Portera-Cailliau, C. *et al.,* 1995). In vitro studies have shown substantial evidence connecting apoptotic pathways and apoptosis with mutant huntingtin (Hickey, M. *et al.,* 2003). Although it is not known how mutant huntingtin promotes cell death, a self-amplification cascade of progressive caspase activation that leads to neuronal dysfunction and eventually cell death has been proposed (Goldberg, Y. *et al.,* 1996; Hickey, M. *et al.,* 2003). Huntingtin is proteolysed by caspase-1 and caspase-3 (Wellington, C.L. *et al.,* 2000; Goldberg, Y. *et al.,* 1996). In HD mouse models and in presymptomatic and early symptomatic stages of HD patients caspase-1 and caspase-3 gene expression is transcriptionally up-regulated (Chen, M. *et al.,* 2000). This leads to an increase of caspase-mediated cleavage of huntingtin and increases the generation of N-terminal huntingtin fragments that are prone to form toxic aggregates in neurons (Ona, V. *et al.,* 1999; Wellington, C.L. *et al.,* 2000; Goldberg, Y. *et al.,* 1996; Hackam, A.S. *et al.,* 1998), while depleting wild type huntingtin (Ona, V. *et al.,* 1999; Sanchez, I. *et al.,* 1999; Kiechle, T. *et al.,* 2002). It appears that some features of HD result from the depletion of huntingtin protein function, whereas recent data have shown that the consequent N-terminal toxic fragments themselves may exert toxic effects on the cell by transcriptional disrupting of other genes (Landles, C. *et al.,* 2004; Hickey, M. *et al.,* 2003; Nucifora, F.C., Jr. *et al.,* 2001). This evidence suggests that caspases are not only mediators of cell death but also of cell dysfunction, possibly more important for HD pathogenesis than for apoptotic cell death alone. Moreover, in human HD striatal brain tissue, activation of several pro- apoptotic proteins, such as Bax, caspases 1, 3, 8, and 9 and release of cytochrome c have been demonstrated (Ona, V. *et al.,* 1999; Sanchez, I. *et al.,* 1999; Kiechle, T. *et al.,* 2002; Vis, J.C. *et al.,* 2005). Despite this, morphological evidence of apoptotic neuronal death in human HD is scarce. Which pathways are involved in apoptosis remains unclear. In this thesis, we studied apoptotic cell death and the expression of apoptotic markers in animal models of HD and in human HD brains that may contribute to the slowly developing death of medium-sized spiny GABAergic projection neurons in the striatum.

IV. Neurochemistry of Hutington's Disease

Neurochemical alterations in HD have long attention from researchers. The pathological changes in HD are caused by neurochemical. Neurochemical alterations are the essential mediators of Huntington's disease pathogenesis which not only produce the characteristic clinical symptoms of HD but also accelerate the process of cell death (Browne SE, *et al*., 1999).

V. Genetics of HD

The disease gene for HD, huntingtin, was identified in 1993 and it encodes a large protein (348kDa) with a polyglutamine stretch named huntingtin (Htt) (Sawa A, *et al*., 2003 and The Huntington's Disease Collaborative Research Group: 1993). Genetic defect in HD is an expansion of an unstable CAG repeats encoding polyglutamines at the 5' end of a huntingtin [also termed "interesting transcript 15" (IT15)] gene on chromosome (Hickey MA, *et al*., 2003). The biological function of the huntingtin protein is still unknown; it is known that the alteration of this protein ultimately results in HD (Bao J, *et al*., 1996 and Reddy, 1999).

Estimates of the prevalence of HD range from 4.1-8.4 per 100,000 people. In the United States, it is estimated that 25000 individuals have HD with another 125,000 individuals at risk (Harper PS.1986). In India: A recent study on the distribution of C-A-G repeats in the normal population suggests a higher prevalence of HD in India closer to that seen in Western Europe. Based on the results, haplotype analysis suggested the presence of a founder mutation in a subset of families and provide evidences for multiple and geographically distinct origins for HD mutation in India. One of the studies conducted on 124 (94 male and 30 female) elderly patients (aged more than 60 years) in a teaching hospital in India reported that there were 2.4% cases of HD, Parkinson's disease in India (Jha S, *et al*., 2004).

VI. Neuropsychological and Neuropsychiatric Aspects of HD

HD, an inherited neurodegenerative disease, damages specific areas of the brain resulting in movement difficulties as well as cognitive and behavioral changes. The cognitive changes in HD have traditionally been referred to as dementia. People with HD have specific and characteristic cognitive difficulties, with other aspects of cognitive function remaining well preserved. Behavioral changes are a characteristic feature of HD and are often the most distressing aspect of the condition for individuals and families dealing with HD (Harper PS.1986). Behavioral changes associated with HD Psychomotor function - Early motor signs of HD typically include the gradual onset of clumsiness, balance trouble, tremor and brief random, fidgeting movements. The primary involuntary movement abnormality and often the earliest symptom, is chorea or choreoathetosis, continuous and irregular writhing and jerking movements (Van Raamsdonk JK, *et al*., 2005). Many HD patients develop a distinctive manner of walking (gait) that may be unsteady, disjoined, or lurching as disease progresses (Delval A, 2006 and Naarding et al., 2001). Frustration, Irritability, Aggression & Anxiety- People suffering from HD may remain even-tempered; others may lose the ability to control their emotions. Emotional volatility may evident in increased irritability or episodes of explosiveness (Van Raamsdonk *et al*., 2005). These individuals may become irritable, frustrated or aggressive if demands are not met. Anxiety, a behavioral symptom of HD, is characterized by nervousness, restlessness, fidgeting, shallow breathing, sweating, fear, and panic rapid heart rate (Klivenyi P, *et al*., 2006). For individuals with HD, continual life changes as HD progresses can be a source of anxiety. Depression is often dismissed as an understandable reaction being diagnosed with HD (Paulsen JS, *et al*., 2005). Altered Sexuality - A very common behavioral symptom of HD is altered sexuality. Possible cause is that the delicate balance of hormones in the brain is disrupted by the progression of HD causing changes in behaviors regulated by hormone levels. Most commonly, people with HD suffer from a decreased sex drive. Increased sex drive and inappropriate sexual behavior are less common alterations of sexuality resulting from HD (Cummings JL. 1995). Cognitive changes in HD, The term "cognitive" refers to tasks of the brain that involve knowing, thinking, remembering, organizing and judging. Cognitive changes in the HD may be due to the disruption of striatal –frontal circuits (Baudic S, *et al*., 2006) Memory and Visual spatial ability an individual suffering from the cognitive symptoms of HD may have memory difficulties. Several investigators have shown that memory recall is generally affected more than memory storage in HD (Baudic S, *et al*., 2006). It is important to note that the memory problems that can occur in people with HD are different from the memory difficulties that can occur in people with Alzheimer's disease (AD) (Lundervold AJ, *et al*., 1994). Most commonly, the individual suffering from cognitive symptoms of HD is aware of his or her visual spatial impairment. Reading difficulties may also be the result of visual spatial impairment; however, the inability to maintain attention may be a contributing factor as well (Anderson KE, *et al*., 2005).

VII. Management of HD

Huntington's disease is a devastating neurological disorder without effective treatment. There is an urgent need for developing effective therapies for HD.

VIII. Treatment of Chorea

Dopamine blocking or dopamine depleting medications Increase dopamine level plays a major role in the pathogenesis of HD. On the basis of these reports dopamine-depleting drug like Tetrabenzine was also used for the treatment of chorea in clinical trial (Hannan JA. 2004). But due to lot of side effects the FDA did not approve this drug. Glutamate antagonism Excitotoxicity is the major cause of death of neurons in the HD. Increase in glutamate release activate the NMDA

receptors and increase the level of Ca 2+ and cause neurotoxicity. The drugs, which block the NMDA receptors, may be useful to decrease the symptoms of HD (Verhagen ML, et al., 2002). GABAergic modulation GABA an inhibitory neurotransmitter is decreased in the HD brain and cerebrospinal fluid. Indeed the GABA mimetic drugs and GABA transminase inhibitors are also be used in the clinical trial for the treatment of HD (Bonelli MR, et al., 2004). Cannabinoids receptor agonists In the brain the cannabinoids and their receptors behave as neurotransmitters or neuromodulators in a variety of processes, such as the regulation of motor behaviour, cognition, learning, memory and antinociception. It is also reported that the cannabinoid receptors are destroyed in the basal ganglia (Becker LI, et al., 2003). Therefore the treatment with cannabinoids could be beneficial for HD. Antioxidants One component of excitoxicity in HD is oxidative stress and antioxidants may therefore have therapeutic utility. A novel antioxidant, BN-82451 improved motor ability and survival and ameliorated neurodegenration in R6/2 HD mice (The Huntington's Disease Collaborative Research Group: 1993 and Hannan JA. 2004).

a) Neurodegeneration and Huntington's Disease

Neurodegeneration diseases have been characterized by progressive dysfunction and death of cells that affect specific neural systems. Neuronal loss is associated with misfolding and aggregation of proteins leading to accumulation of abnormal extracellular and intracellular filamentous deposits in specific cells types, mainly neurons and glia, representing the features of many neurodegeneration disorder (Mattson, 2006). Common pathogenic mechanism which cause neurodegeneration disorders are:

1. Oxidative stress and formation of free radicals / reactive oxygen species (ROS).
2. Mitochondrial dysfunction.
3. Neuroinflammatory dysfunction / neuro-immune response.
4. Abnormal protein dynamics with protein misfolding, defective protein degradation and aggregation.

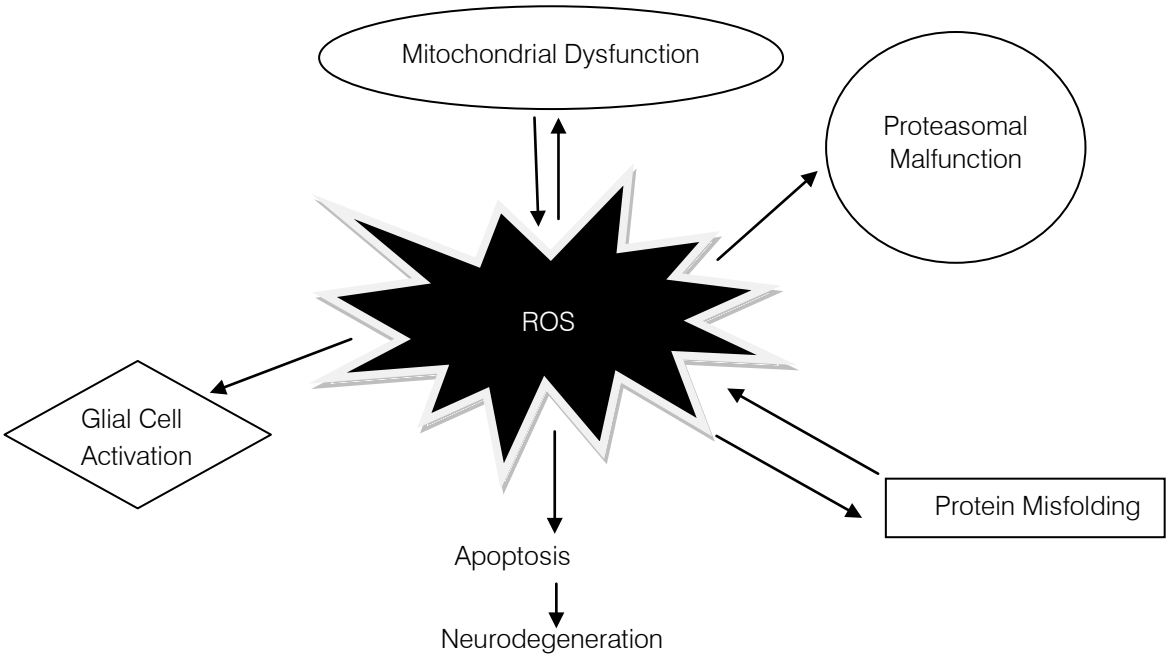


Fig. 2: Different mechanism leading to neurodegeneration

Dysfunction of mitochondrial energy metabolism leads to reduced ATP production, impaired calcium puffering, and generation of reactive oxygen species (ROS). Generation of reactive oxidants, including ROS is increased in damaged mitochondrial and in cells with compromised mitochondrial function.

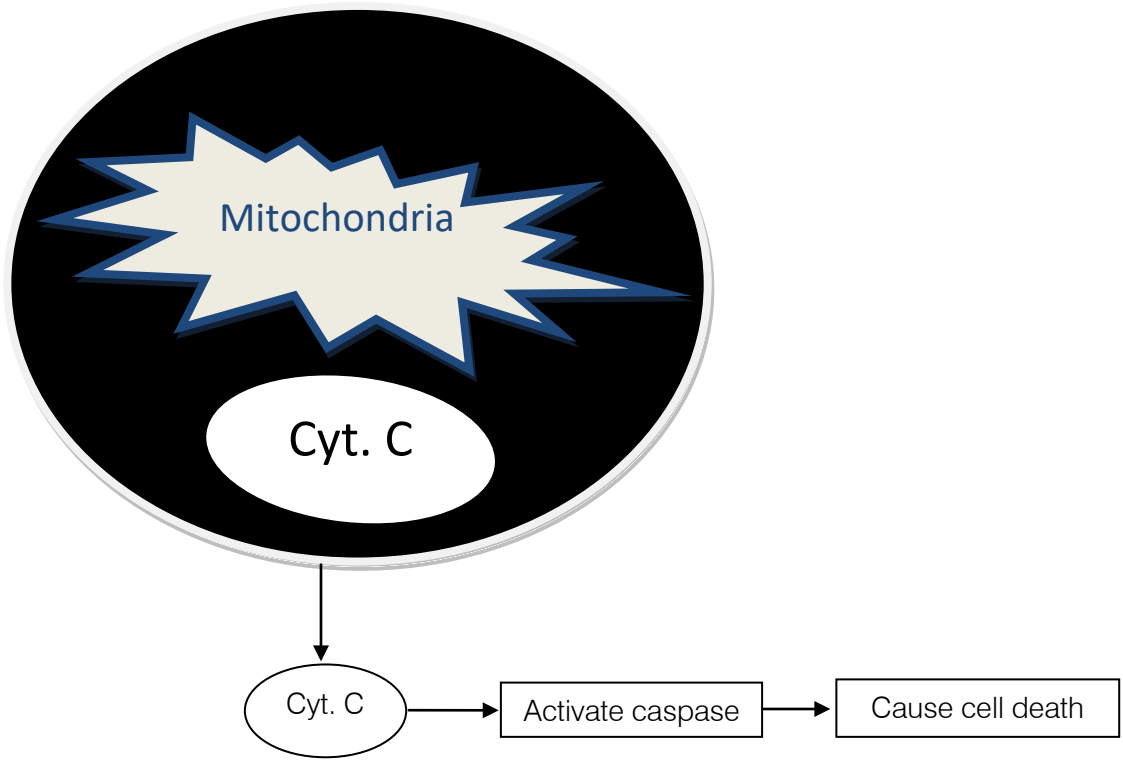


Fig. 3: Cascade leading to neuronal death related to mitochondria defects

Acute exposure of high levels of oxidant can induce the mitochondrial permeability transition (MPT), uncouple oxidative phosphorylation with catastrophic effect on mitochondrial energetics and contribute to cytotoxicity via necrosis or apoptosis through release of cytochrome c etc (Kwong JQ,2006).

On the other hand proteasomal inhibition reduced mitochondrial complex 1 and 11 activities, increased mitochondrial reactive oxygen species (ROS) production and increased the presence of damage production in autophogosomes (Sullivan P,2004).

IX. Inflammation and Huntington's Disease

Inflammation in the brain and the rest of the central nervous system (CNS) is a key factor in neurodegenerative diseases. Inflammation plays a significant role in the progression of HD. The previous Studies of the HD brain indicate that long-term inflammation plays a significant role in the progression of HD. It is suggested that excitotoxic amino acids such as glutamate induce a direct activation and proliferation of cells involved in inflammation. Since glutamate activity is also implicated in the progression of HD, it is possible that the glutamate molecules in the HD brain induce an inflammatory response (Arzberger T, et al., 1997). One of the first steps in excitotoxic neuronal damage involves the hyperstimulation of N-methyl-D-aspartate (NMDA) receptors leading to a massive calcium influx that activates, among other processes, the calcium dependent phospholipase A2 (PLA2). Further, PLA2 cleaves membrane phospholipids to yield arachidonic acid (AA), a free fatty acid, which is converted by cyclooxygenases (COX) into prostaglandins (PGs). The inflammatory response results in the activation of various types of cells and the production of different molecules that can lead to cell death (Kukreja RC, et al., 1986).

An example of cells activated by the inflammatory response is the microglia (a type of immune cell), which have been found to be highly activated in the HD brain. Research has shown that there is an activated microglia is found along the vicinity of nerve cells that contain neuronal inclusions (NIs) – accumulation of the huntingtin protein. This finding suggests that the huntingtin protein accumulation influences the activation of reactive microglia. Nerve cell injury due to excitotoxins such as glutamate also induces long-term microglial activation in the brain (Arzberger T, et al., 1997 and Kukreja RC, et al., 1986).

Neuro-inflammation is mediated by soluble pro-inflammatory molecules such as cytokines, prostaglandins and nitric oxide (N.O) (Silvestroni *et al.,* 2009). While some mediators such as IL, TNF-α were increased in striatum and some mediators such as IL-6, IL-8 were also upregulated in cortex .Microglia, the resident immune cells of the CNS, play a critical role in inflammation-mediated neurodegeneration. An example of cells activated by the inflammatory response is the microglia, which has been found to be activated in the HD brain. Normally, microglia cells in their resting state vigilantly monitor the health of neurons. In brain damage

or infection, microglia cells become activated and may secrete a variety of inflammatory mediators and neurotoxic factors. Activated microglia cells trigger and maintain an inflammatory response, deluging neurons with a whole host of inflammatory mediators that may ultimately lead to neuronal cell death. Neurodegenerative CNS diseases, including Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), amyotrophic lateral sclerosis (ALS), and age-related macular degeneration (ARMD), are all associated with chronic neuro-inflammation and elevated levels of several cytokines. Microglial activation and chronic inflammation thereafter is the starting point for elevated levels of a wide array of potentially neurotoxic molecules including pro-inflammatory cytokines, proteinases, and reactive oxygen species (ROS) (Boje, K *et al.,* 1992, Chao et al., 1995, Chao *et al.,* 1992, Jeohn *et al.,* 1998 and Xie *et al.,* 2002). Suppression of microglial production of neurotoxic mediators will result in neuroprotection (Glass *et al.,* 2010 and Ransohoff, R *et al.,* 2009).

a) Oxidative Stress in HD

HD is an autosomal dominantly inherited progressive neurodegenerative disorder, affecting people in middle age. HD is characterized by the progressive development of involuntary choreiform movements, cognitive impairment, neuropsychiatric symptoms, and premature death. The etiology of HD is unknown, but increasing evidence suggests important roles of altered gene transcription, mitochondrial dysfunction, excitotoxicity, and oxidative stress (Gardian, G, *et al.,* 2004). Oxidative stress has been implicated in the neural dysfunction and death observed un neurodegenerative conditions such as Alzheimer's disease (AD) (Butterfield *et al.,* 2002a; Buterfield *et al.,* 2002b), Parkinson's disease (PD) (Blum *et al.,* 1997), as well as HD (Browne et al., 1999; Goswami *et al.,* 2006; Chen *et al.,* 2007). Cells normally produce free radicals as by products of aerobic respiration and other metabolic processes (Grunewald *et al.,* 1999). These free radicals include reactive oxygen species (ROS). ROS are highly reactive oxidant and can have deleterious effects on cellular lipids, proteins, and DNA. Cells normally have enzymes and coenzymes that act as antioxidant. These are able to neutralize ROS and prevent them from causing damage (Heales *et al.,* 2002). ROS include the superoxide anion (O_2^-), hydrogen peroxide (H_2O_2), nitric acid (NO) and hydroxyl radicals (OH) (Keller *et al.,* 2001). The primary site of the production of these free radicals is the mitochondrion (Fleury *et al.,* 2002). Superoxide is produced within the mitochondrion at complexes 1, 11, 111 and 1V of the electron transport chain. A single electron is transferred from the electron transport chain at these sites to molecular oxygen. The reaction of superoxide with H^+ catalyzed by superoxide dismutase (SOD) produces H_2O_2 (Keller et al., 2001; Klein et al., 2003). H2O2 reacts with the transition metals cu+ or Fe2+ via the Fenton reaction to produce the hydroxyl radical. NO is produced by nitric oxide synthase (NOS), which catalyzes the conversion of arginine to citrulline and NO. NO can react with superoxide to produce the Peroxynitrite free radicals (Deckel *et al.,* 2001).

Oxidative stress is defined as the imbalance between biochemical processes which are responsible for the production of reactive oxygen species (ROS) and those responsible for removal of ROS *(Browne S et al., 1997).* Oxidative Stress is the common denominator of the disease. HD is widely distributed in both neurons and extraneuronal tissues. Oxidative Stress plays an important role in HD pathogenesis. In Huntington's disease, the damage caused by oxidative stress includes lipid peroxidation, protein oxidation and DNA oxidation. 8-hydroxydeoxyguanaise (8-OHdn), an oxidized DNA marker which increased in the caudate of the HD patients *(Browne S et al., 1997).* The increased level of 8-OHdn in mitochondrial DNA of the parietal cortex was found in late stage of HD (Polidori M, *et al.,* 1999). Several studies have documented increased oxidative damage to DNA outside the brain of Huntington's disease patients by demonstrating increased 8- OHdn in HD peripheral blood (Chen C, *et al.,* 2007 *and* Hersch S *et al.,* 2006). Oxidative stress caused by N-terminal fragments of mutant htt which can be suppressed by over-expression of heatshock proteins in a HD cellular model.Oxidative stress could promote htt aggregation and mutant htt induced cell death by impairing proteosomal function. Oxidative damage has been associated with neuronal loss in HD (Goswami A *et al.,* 2006). These data indicate a role for oxidative stress in mediating HD and this may be alleviated by antioxidant therapy.

X. Development of Novel Therapeutics for HD

HD is a progressive disorder with fatal outcome. At present there are no effective treatments. Since the identification of the HD gene in 1993, great advancement in the understanding of the molecular biology and pathophysiology of the disorder has been occurred. The advances have suggested a new therapeutics strategy aimed at slowing disease progression or forestalling the onset of this devastating neurodegenerative disease. The treatment option available for HD are symptomatic which focus on neurological and psychiatric symptoms and aim to improve quality of life (Boneli and Hoffman, 2007). Agents that inhibit mutant huntingtin aggregation and Transglutaminase inhibitors. The huntingtin aggregates and inclusions play a major role in the pathogenesis of HD. Inhibit mutant huntingtin from aggregation would provide a way to prevent the progression of the disease

(Aiken CT, *et al.,* 2004). Transglutaminase (TGase) can use huntingtin as a substrate to cross-link huntingtin molecules. TGase activity was found to have increased in HD postmortem brains (Karpuj MV, et al., 2002). Cystamine is an inhibitor of TGase and showed a small but significant neuroprotective effect with improvement of motor function, survival and loss of bodyweight. Protease inhibitors Recent findings showed that huntington could be cleaved by proteases, including caspases, calpain, and aspartyl protease. Caspase and calpain-mediated partial cleavage of mutant huntingtin promotes huntingtin aggregation and cellular toxicity, inhibitors of huntingtin partial cleavage might have therapeutic values. Caspase inhibitors, z-VAD-fmk and z-DEVD- fmk, can prevent cleavage of huntingtin by caspases and reduce cytotoxicity caused by expanded polyglutamine tract (Chen M, et al., 2000). Caspase inhibitor minocycline was able to inhibit huntingtin aggregation, retard disease progress and prolong the lifespan of HD mice. Protease inhibitors could reduce N-htt fragments and in turn, prevent or delay disease progression (Wang X, et al., 2003). Histone deacetylase (HDAC) inhibitors Inhibitors of histone deacetylase (HDAC) can increase gene transcription and have been examined as a potential therapy in both HD Drosophila and transgenic R6/2 HD mice. Suberoylanilide hydroxamic acid (SAHA), a selective HDAC inhibitor, reduced neurodegeneration in HD Drosophila (Steffan JS, et al., 2001).

a) Other Neuroprotective Approaches Gene Therapy

Intracellular antibodies (intrabodies) and RNA interference (RNAi) are two potential methods that could be used for gene therapy of HD. Mitochondria dysfunction has been implicated in HD pathogenesis. Therefore, compounds enhancing energy metabolism have been evaluated for treatment of HD. Coenzyme Q10 and creatine are neuroprotective, putatively via enhancing cerebral energy metabolism (Browne SE, *et al.,* 1999; Qin ZH, *et al.,* 2004). Neural cell transplantation is also under development for the treatment of HD. Brain derived Neurotrophic factors: Brain derived neurotropic factor (BDNF) expression is reduced in the caudate and putamen of patients with HD. That enhanced expression of neurotropic factors may mitigate the effects of neurotoxins and thus be a potential therapeutic strategy was explored in animal and cell models (Bemelmans AP, et al., 1999 and Davis JD, et al., 2001).

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